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产品名称: **Cariprazine**
产品别名: 卡利拉嗪; **RGH-188**

生物活性:	
Description	Cariprazine is a novel antipsychotic drug candidate that exhibits high affinity for the D ₃ (K _i =0.085 nM) and D ₂ (K _i =0.49 nM) receptors, and moderate affinity for the 5-HT _{1A} receptor (K _i =2.6 nM).
IC ₅₀ & Target	K _i : 0.49 nM (D ₂ receptor), 0.085 nM (D ₃ receptor), 2.6 nM (5-HT _{1A} receptor)[1]
In Vitro	Cariprazine stimulates inositol phosphate (IP) formation with a high potency (pEC ₅₀ 8.5) with relatively low efficacy (E _{max} 30%)[2]. Cariprazine, a novel candidate antipsychotic, demonstrated approximately 10-fold higher affinity for human D ₃ versus human D _{2L} and human D _{2S} receptors (pK _i 10.07, 9.16, and 9.31, respectively). Cariprazine displays high affinity at human serotonin (5-HT) type 2B receptors (pK _i 9.24) with pure antagonism. Cariprazine has lower affinity at human and rat hippocampal 5-HT _{1A} receptors (pK _i 8.59 and 8.34, respectively) and demonstrates low intrinsic efficacy. Cariprazine displays low affinity at human 5-HT _{2A} receptors (pK _i 7.73). Moderate or low affinity for histamine H ₁ and 5-HT _{2C} receptors (pK _i 7.63 and 6.87, respectively) suggest Cariprazine's reduced propensity for adverse events related to these receptors[2]. Cariprazine is over sixfold more potent (EC ₅₀ =1.4 nM) than Aripiprazole (EC ₅₀ =9.2 nM) in inhibiting isoproterenol-induced cAMP production in HEK-293 cells[4].
In Vivo	Administration of Cariprazine (30 µg/kg) reduces the striatal uptake of both radioligands to the level of nonspecific binding compared with baseline PET measurements. Cariprazine has negligible effect on the time-activity curves in the cerebellum. At doses of 5.0 and 30 µg/kg, Cariprazine causes a dose-dependent dopamine D ₂ /D ₃ receptor occupancy of ~45% and ~80% for both antagonist [¹¹ C] raclopride and agonist radioligand [¹¹ C]MNPA. Receptor occupancy of dopamine D ₂ /D ₃ receptors calculated using the transient equilibrium and the MRTM2 methods ranged from 5% at the lowest dose (1.0 µg/kg) to 94% at the highest dose (300 µg/kg)[1]. The effects of 5 doses of Cariprazine (ranging from 0.005 to 0.15 mg/kg) are examined on EPM behavior of wild-type mice. Whereas lower doses of Cariprazine (0.005 to 0.02 mg/kg) do not alter the time spent in open arms, the two higher doses (0.08 and 0.15 mg/kg) lead to a significant decline of this measure (ANOVA, (F(5,52)=4.20; p=0.0032)). Moreover, the two higher doses of Cariprazine also lead to a significant decrease in the total number of arm entries (F(5,52)=7.21; p=0.0001)) but this decrease in the total number of arm entries is largely accounted for by a significant decrease in the number of closed arm entries (F(5,52)=11.75; p=0.0001)). The two highest doses of Cariprazine (0.08 and 0.15 mg/kg) have significant effects on locomotor activity, but doses ranging from 0.005 to 0.02 mg/kg do not affect anxiety-like behavior or locomotor activity in the EPM test[3]. A significant (P<0.01) reduction in ouabain-induced hyperactivity is observed after acute i.p. administration of all doses of Cariprazine (mean±SEM: 0.06 mg/kg, 64.2±3.88; 0.25 mg/kg, 72.7±11.67; 0.5 mg/kg, 40.6±5.32; 1 mg/kg, 19.5±8.78) and lithium (40.4±12.78), compared with ouabain injection alone (114.6±14.33). The highest Cariprazine dose produced significant sedation (72% inhibition for Cariprazine 1.0 mg/kg aCSF vs. saline aCSF; P<0.05)[4].
	[1]. Seneca N, et al. Occupancy of dopamine D ₂ and D ₃ and serotonin 5-HT _{1A} receptors by the novel antipsychotic drug candidate, cariprazine (RGH-188), in monkey brain measured using positron emission tomography. Psychopharmacology (Berl). 2011 Dec;218(3):579-8 [2]. Kiss B, et al. Cariprazine (RGH-188), a dopamine D(3) receptor-preferring, D(3)/D(2) dopamine



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References	<p>receptor antagonist-partial agonist antipsychotic candidate: in vitro and neurochemical profile. J Pharmacol Exp Ther. 2010 Apr;333(1):328-40.</p> <p>[3]. Zimnisky R, et al. Cariprazine, a dopamine D(3)-receptor-preferring partial agonist, blocks phencyclidine-induced impairments of working memory, attention set-shifting, and recognition memory in the mouse. Psychopharmacology (Berl). 2013 Mar;226(1):91-100</p> <p>[4]. Gao Y, et al. Cariprazine exerts antimanic properties and interferes with dopamine D2 receptor β-arrestin interactions. Pharmacol Res Perspect. 2015 Feb;3(1):e00073.</p>
实验参考:	
Cell Assay	<p>Cells are seeded on a 24-well tissue culture plate in 500 μL of medium. Fifty microliters of medium containing 0.55 μCi myo-[3H]inositol is added (final concentration 1 μCi/mL) and incubated for 18-20 h. Cells are then washed three times with buffer containing 140 mM NaCl, 5 mM KCl, 2 mM CaCl_2, 5 mM HEPES, 5 mM Na-HEPES, 20 mM glucose, and 10 mM LiCl (pH 7.4). Cells are then incubated for an additional 60 min (37°C) in medium with test compounds alone (agonist test) or alongside 1000 nM (\pm)-Quinpirole (antagonist test). Medium is then aspirated off, cells are lysed by adding 400 μL of 0.1 M HCl/2 mM CaCl_2, and supernatants are frozen at -72°C. After thawing and centrifugation at 1000g for 10 min, 200 μL of each supernatant is loaded on 250 μL of AG1-X8 (formate form) anion exchange column. Effluent is discarded, and columns are washed twice in 1.5 mL of distilled water. IPs are eluted with 2.5 mL of 1 M ammonium formate/0.1 M formic acid directly into scintillation vials, 10 mL of Optiphase HiSafe 3 is added, and the radioactivity is determined in a TriCarb 4900 scintillation counter[2].</p>
Animal Administration	<p>Mice[3]</p> <p>Experiments are performed on wild-type C57Bl/6J mice. In tests of cognitive functions, it is essential to employ concentrations of drugs that have no effects on emotional behavior and that do not impair locomotor activity. Whether Cariprazine (administered at a dose range of 0.005 to 0.15 mg/kg) is first tested affected the behavior of mice in the EPM, a test of anxiety-related behavior that is also critically dependent upon normal locomotor activity. Animals are exposed to an EPM apparatus designed for mice (leg height: 45 cm, arm length: 35 cm, lane width: 5 cm, wall height: 15 cm). Testing (under 100 lux lighting) is performed between 1 and 4 PM. Mice are placed in the center of the maze and their time spent in open arms and the number of closed and open arm entries during a 5 min test period is recorded. Measures of the time spent in open arms and the number of open arm entries served as a measure of anxiety-like behavior. The number of closed arm entries served as a measure of locomotor activity.</p> <p>Rats[4]</p> <p>Adult male Sprague-Dawley rats (150-300 g) are used. Cariprazine is dissolved in 0.9% saline and administered at 0.06, 0.25, 0.5, and 1.0 mg/kg via intraperitoneal (i.p.) injection 1 h before i.c.v. injection of ouabain and daily thereafter for 7 days. Open field activity is assessed immediately following the i.c.v. injection and again after 7 days (the activity is noted 10-14 h after the last i.p. injection of Cariprazine).</p>
	<p>These assays are done in 50 mM Tris (pH 7.4), 100 mM NaCl, 7 mM MgCl_2, 1 mM EDTA, and 1 mM DTT. Assay tubes (final volume 250 μL) contain 50 μM (striatum and hippocampus) or 1 μM (D_2 and D_3 cell membrane) GDP, the ligand to be examined, and membrane suspension (250 μg tissue/tube</p>



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Kinase Assay	for the striatum and hippocampus and 20 µg protein/tube for hD ₂ and hD ₃ membranes). Samples are preincubated for 10 min at 30°C. After the addition of 50 pM [³⁵ S]GTPγS, membranes are incubated for an additional 60 min at 30°C. Nonspecific binding is determined in the presence of 10 µM GTPγS; basal binding is determined in the presence of buffer only. The assay is terminated by rapid filtration through UniFilter GF/B using a harvester, and the membranes washed four times with 1 mL of ice-cold buffer. After drying (40°C for 1 h), 40 µL of Microscint is added to the filters, and the bound radioactivity is determined by a TopCount NXT counter[2].
References	<p>[1]. Seneca N, et al. Occupancy of dopamine D2 and D3 and serotonin 5-HT1A receptors by the novel antipsychotic drug candidate, cariprazine (RGH-188), in monkey brain measured using positron emission tomography. <i>Psychopharmacology (Berl)</i>. 2011 Dec;218(3):579-8</p> <p>[2]. Kiss B, et al. Cariprazine (RGH-188), a dopamine D(3) receptor-preferring, D(3)/D(2) dopamine receptor antagonist-partial agonist antipsychotic candidate: in vitro and neurochemical profile. <i>J Pharmacol Exp Ther</i>. 2010 Apr;333(1):328-40.</p> <p>[3]. Zimnisky R, et al. Cariprazine, a dopamine D(3)-receptor-preferring partial agonist, blocks phencyclidine-induced impairments of working memory, attention set-shifting, and recognition memory in the mouse. <i>Psychopharmacology (Berl)</i>. 2013 Mar;226(1):91-100</p> <p>[4]. Gao Y, et al. Cariprazine exerts antimanic properties and interferes with dopamine D2 receptor β-arrestin interactions. <i>Pharmacol Res Perspect</i>. 2015 Feb;3(1):e00073.</p>